Exhibit 1

SYNTHESIS

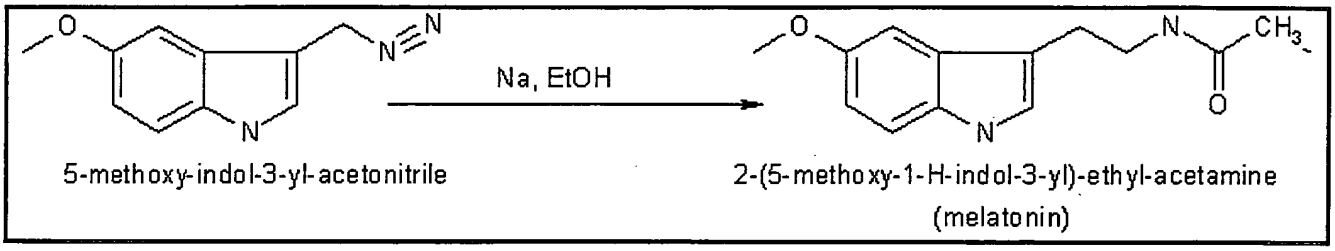
Chemical Synthesis of Melatonin

The methods for the chemical synthesis of melatonin are generally not so complicated and do not involve more than three steps of conversion. Three synthesis reactions of melatonin from primary literatures are shown below;

Reaction 1*

In 1958 melatonin was first isolated and characterised by A.B.Lerner. It was know as one of a substituted 5-hydroxyindole derivative in the pineal gland that could lighten pigment cells. It had not been know to exist in biological tissue although it had been isolated as a urinary excretion product in rats after administration of 5-hydroxytryptamine*.

Melatonin or N-acetyl-5-methoxytryptamine (40 mg) was prepared by reducing 100 mg of 5-methoxyindole-3-acetonitrile with 160 mg of sodium and 2 ml of ethanol. Then the product was acetylated with 4 ml of both glacial acetic acid and acetic anhydride at 100 °C for 1 minute. Purification was achieved by countercerrent distribution and silicic acid chromatography.

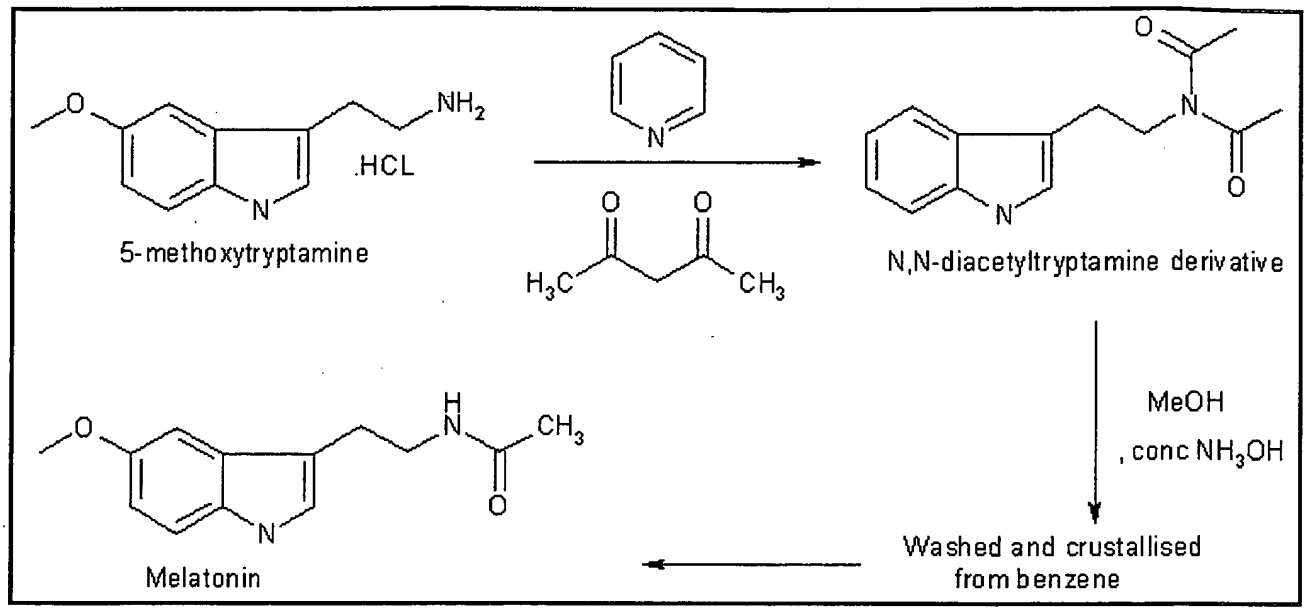


5-methoxy-indol-3-yl-acetonitrile

2-(5-methoxy-1-H-indol-3-yl)-ethyl-acetamine (melatonin)

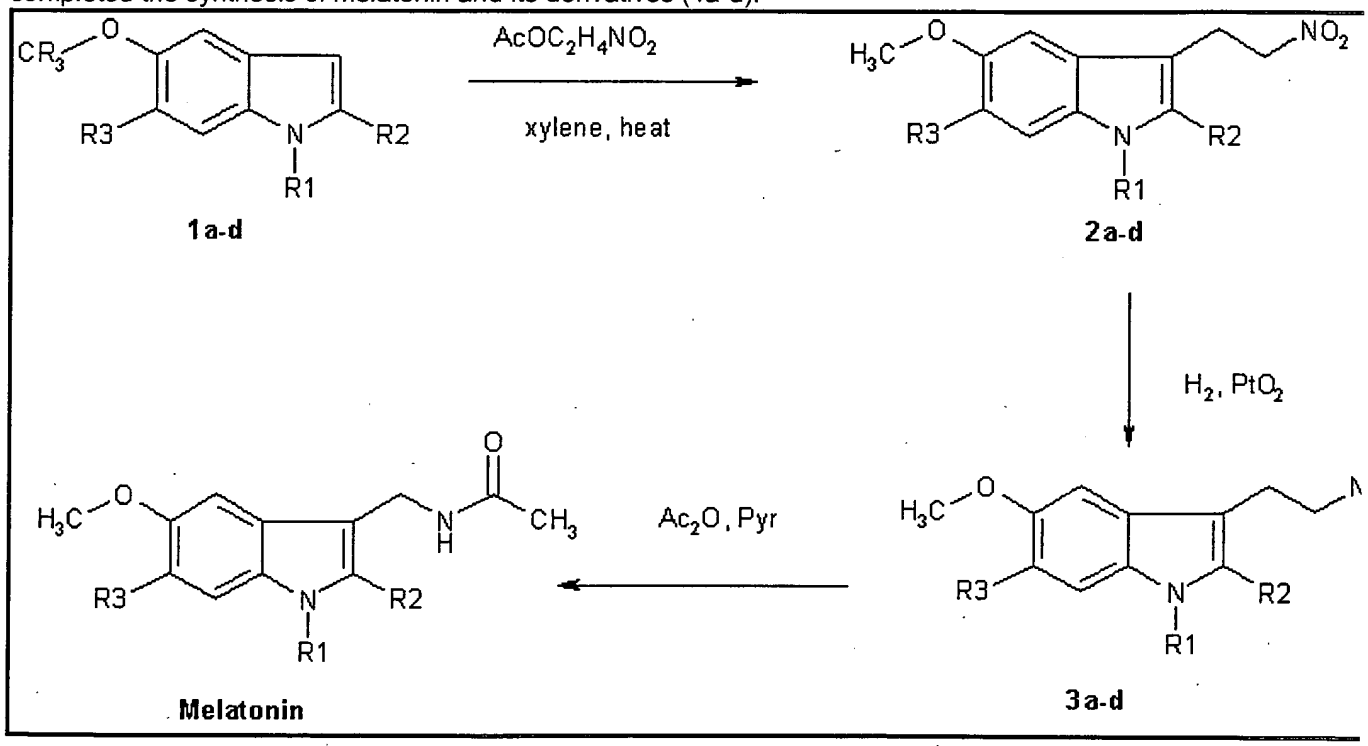
Reaction 2*

5-Methoxytryptamine hydrochloride (1g, 4.75 mmole) was dissolved in pyridine (10 ml) and acetic anhydride (10 ml) and kept overnight at 20 °C. The solution was poured onto iced, neutralised with dilute hydrochloric acid and extracted with chloroform (2x25 ml). The combined extracts were washed with water, dried in $MgSO_4$ and evaporated to afford a liquid of N,N diacetyltryptamine derivative. The liquid was then poured into water (50 ml) and extracted with chlroform (2x25 ml). The combined organic layers were washed with water (25 ml), dried in $MgSO_4$ and evaporated to dryness. The residual solid crystallised from benzene to afford melatonin 819 mg, 80% yield.



Reaction 3*

The more reactive indoles (1a-1d) were alkylated at the 3 position by reaction with nitroethene generated in situ by thermolysis of nitroethyl acetate. The nitroethyl acetate used for this purpose was prepared by acetylation of nitroethanol with acetic anhydride using NaOAc as a catalyst. These conditions constitute a substantial improvement of the overal yield of the reation. Reduction of the nitroethylated indoles (2a-d) by hydrogenation over PtO_2, followed by acetylation fo the resluting tryptamines with acetic anhydride-pyridine completed the synthesis of melatonin and its derivatives (4a-d).



Biological Synthesis and Metabolism of Melatonin

The biosynthesis of melatonin (Fig.1) is initiated by the uptake of the essential amino acid tryptophan into pineal parenchymal cells. Tryptophan is the least abundant of essential amino acids in normal diets. It is converted to another amino acid, 5-hydroxytryptophan, through the action of the enzyme tryptopahn hydroxylase and then to 5-hydroxytryptamine (serotonin) by the enzyme aromatic amino acid decarboxylase. Serotonin concentrations are higher in the pineal than in any other organ or in any brain region. They exhibit a striking diurnal rhythm remaining at a maximum level during the daylight hours and falling by more than 80% soon after the onset of darkness as the serotonin is converted to melatonin, 5-hydroxytryptophol and other methoxyindoles. Serotonin's conversion to melatonin involves two enzymes that are characteristic of the pineal : SNAT (serotonin-N-acetyltransferase) which converts the serotonin to N-acetylserotonin, and HIOMT (hydroxyindole-O-methyltrasferase) which trasfers a methyl group from S-adenosylmethionine to the 5-hydroxyl of the N-acetylserotonin. The activities of both enzymes rise soon after the onset of darkness* because of the enhanced release of norepinephrine from sympathetic neurons terminating on the pineal parenchymal cells.

Another portion of the serotonin liberated from pineal cells after the onset of darkness is deaminated by the enzyme monoamine oxidase (MAO) and then either oxidized to form 5-hydroxyindole acetic acid or reduced to form 5-hydroxytryptophol (Fig.1). Both of these compounds are also substrates for HIOMT and can thus be converted in the pineal to 5-methoxyindole acetic acid 5-methoxytryptophol (Fig.1). The level of this latter indole, like that of melatonin, rises markedly in the pineal with the onset of darkness. Since 5-methoxytryptophol synthesis does not require the acetylation of serotonin, the nocturnal increase in pineal SNAT activity cannot be the trigger that causes pineal methoxyindole levels to rise. More likely, a single unexplained process- the intraparenchymal release of stored pineal serotonin, which then becomes accessible to both SNAT and MAO. This process ultimately controls the rates at which all three major pineal methoxyindoles are synthesized and generates the nocturnal increases in pineal melatonin and 5-methoxytryptophol. The proportion of available serotonin acetylated at any particular time of day or night depends on the relative activities of pineal SNAT and MAO at that time. The rates of methylation of all three 5-hydroxyindoles formed from pinela serotonin depends on HIOMT activity.

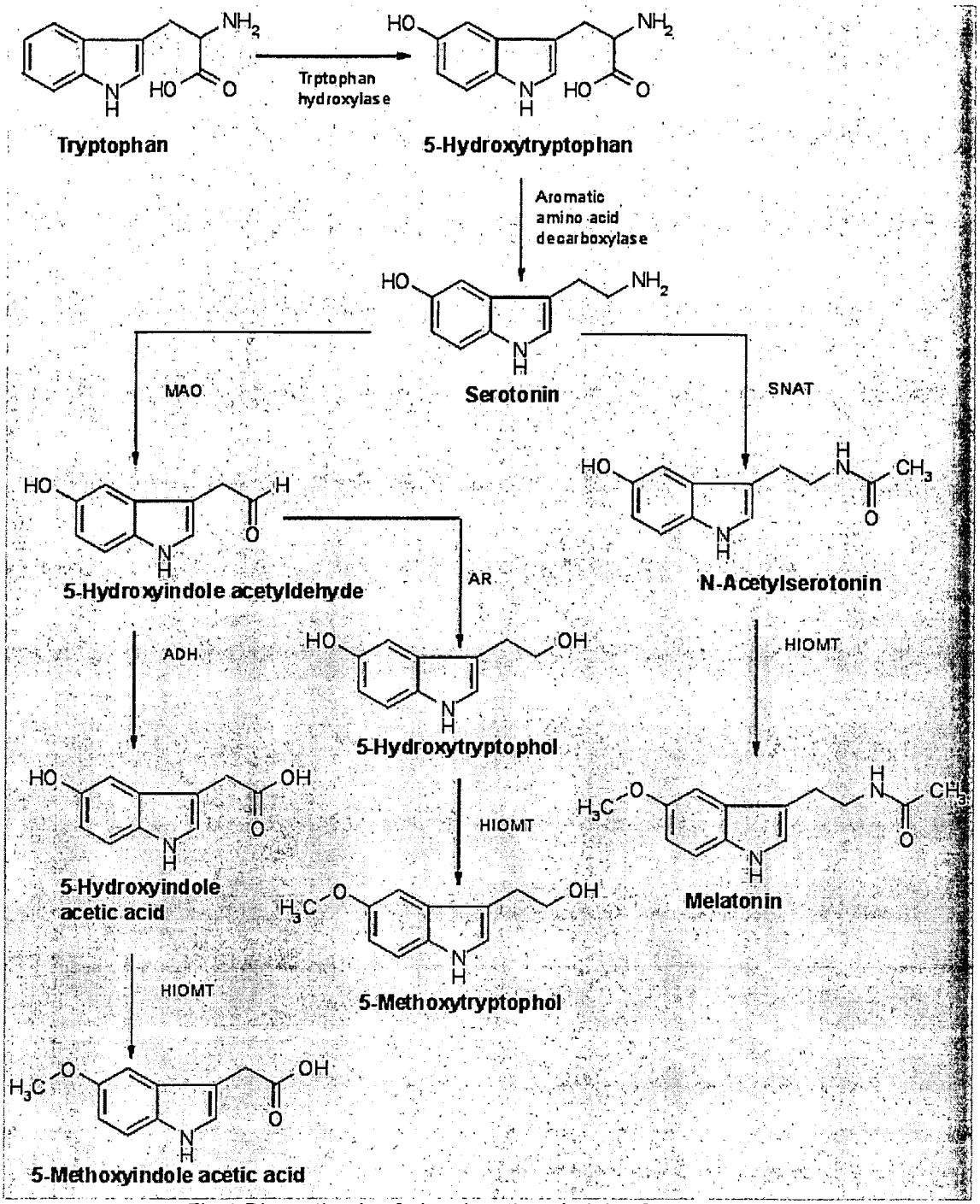


Fig.1 Biosynthesis of pineal methoxyindoles from serotonin

Serotonin may be either acetylated to form N-acetylserotonin through the action of the enzyme serotonin-N-acetyltransferase (SNAT), or oxidatively deaminated by monoamine oxidase (MAO) to yield an unstable aldehyde. This compound is then either oxidized to 5-hydroxyindole acetic acid by the enzyme aldehyde dehydrogenase (ADH), or reduced to from 5-hydroxytryptophol by aldehyde reductase (AR). Each of these 5-hydroxyindole derivatives of serotonin is a substrate for hydroxyindole-O-methyltrasferase (HIMOT). The enzymatic trasfer of a methyl group from S-adenosylmethionine to these hydroxyindoles yields melatonin (5-hydroxy-N-acetyltryptamine), 5-methoxyindole acetic acid and 5-methoxytryptophol respectively. Pineal serotonin is synthesized from the essential amino acid tryptophan by 5-hydroxylation folloed by decarboxylation. The first step in ths enzymic sequence is catalysed by tryptophan hydroxylase. The second step is catalysed by aromatic L-amino acid decarboxylase.

Exhibit 2

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

DRUG THERAPY

The Medical Management of Depression

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RECURRENT EPISODES OF MAJOR DEPRESSION, WHICH IS A COMMON and serious illness, are called major depressive disorder; depressive episodes that occur in conjunction with manic episodes are called bipolar disorder. Major depressive disorder accounts for 4.4 percent of the total overall global disease burden, a contribution similar to that of ischemic heart disease or diarrheal diseases.[1] The prevalence of major depressive disorder in the United States is 5.4 to 8.9 percent[2] and of bipolar disorder, 1.7 to 3.7 percent.[3] Major depression affects 5 to 13 percent of medical outpatients,[4] yet is often undiagnosed and untreated.[5,6] Moreover, it is often undertreated when correctly diagnosed.[6]

The demographics of depression are impressive. Among persons both with major depressive disorder and bipolar disorder, 75 to 85 percent have recurrent episodes.[7,8] In addition, 10 to 30 percent of persons with a major depressive episode recover incompletely and have persistent, residual depressive symptoms, or dysthymia, a disorder with symptoms that are similar to those of major depression but last longer and are milder.[8,9] Patients who have diabetes, epilepsy, or ischemic heart disease with concomitant major depression have poorer outcomes than do those without depression.[10,11] The risk of death from suicide, accidents, heart disease, respiratory disorders, and stroke is higher among the depressed.[12,13] Effective treatment of depression may reduce mortality or improve the outcome after acute myocardial infarction[14] or stroke[15] and lower the risk of suicide.[16]

PATHOPHYSIOLOGICAL FEATURES OF DEPRESSION

The clinical picture of depression varies from one major depressive episode to another in any given patient. This suggests that major depression, despite its various symptom profiles, may have a common underlying cause. If so, the clinically evident symptom profiles may result from differing patterns of neurotransmitter abnormalities in various brain regions.[17] Consonant with such hypotheses, a host of deficiencies — in serotonin, norepinephrine, dopamine, γ-aminobutyric acid (GABA), and peptide neurotransmitters or trophic factors such as brain-derived neurotrophic factor, somatostatin, and thyroid-related hormones — have been proposed as contributing to depression.[18] Furthermore, overactivity in still other neurotransmitter systems involving acetylcholine, corticotropin-releasing factor, and substance P are thought to be implicated in depression.[18] Although no specific abnormalities in genes that control neurotransmitter or hormonal synthesis or release have been identified with certainty, both major depressive disorder and bipolar disorder are clearly heritable.[19] How a genetic predisposition interacts with adverse early-life experience to alter brain development and lead to major depression remains unclear.

Genes and stress are hypothesized to alter neuron size and the extent of neuronal processes, the production of new neurons, and neural repair in major depression.

Elevated cortisol levels, which characterize some moderate-to-severe depressive states, may be associated with a reduction in hippocampal volume, which appears to be proportional to the duration of untreated depression.[20] This process has been likened to a loss of neurons similar to that mediated by corticosteroids in animal models of stress[21] and as suggested by magnetic-resonance-imaging studies that have reported lower levels of *N*-acetyl aspartate, a neuronal marker, in depression.[22]

Major depression in response to stressful situations has been reported as more common among persons harboring a variant in the proximal 5′ regulatory region of the gene encoding the serotonin-transporter protein (5-HTT) (the target of selective serotonin-reuptake inhibitors [SSRIs]) that modifies promoter activity. This variant, in the *5-HTT* gene–linked promoter region (*5-HTTLPR*), modifies promoter activity and is associated with lower transcriptional efficiency of the *5-HTT* gene, ultimately leading to fewer copies of the messenger RNA encoding the serotonin-transporter protein.[23] This lower-expressing variant may be associated with the amygdala-mediated hyperresponsiveness of young children to frightened or frightening faces that can facilitate encoding of painful memories, leading to stress sensitivity in adulthood.[24] This variant is also associated with a reduction of serotonin function in response to maternal deprivation in nonhuman primates, an effect that persists into adulthood.[25] An induced functional deficiency of the 5-HTT protein that is confined to the early postnatal period in mice results in altered behavior when they are grown, indicating possible changes in brain development that affect adult behavior.[26]

Brain imaging has identified numerous regions of altered structure or activity in the brain during major depression, suggesting disordered neurocircuitry in a variety of structures, such as the anterior and posterior cingulate cortex; the ventral, medial, and dorsolateral prefrontal cortex; the insula; the ventral striatum; the hippocampus; the medial thalamus; the amygdala; and the brain stem.[17] These brain areas regulate emotional, cognitive, autonomic, sleep, and stress-response behaviors that are impaired in mood disorders. Studies with the use of positron-emission tomography indicate a decrease in serotonin transporters as well as altered postsynaptic serotonin-receptor binding in many of the same brain regions, suggesting altered circuitry congruent with serotonin-system abnormalities.[27]

DIAGNOSIS OF A MAJOR DEPRESSIVE EPISODE

Diagnosis of major depression is based on standard clinical criteria such as those published by the American Psychiatric Association.[28] The criteria for the diagnosis of an episode include at least two weeks of depressed mood, loss of interest, or diminished sense of pleasure plus four of seven other features that are sufficient to cause clinically important psychological or physical distress or functional impairment. These features include a weight change of 5 percent or more in one month or a persistent change in appetite, insomnia or hypersomnia on most days, changes in psychomotor state, fatigue, feelings of guilt and worthlessness, diminished concentration and decisiveness, and suicidal ideation or a suicide attempt. First or "early" depressive episodes are often milder than are episodes of returning depression, and an earlier age at onset generally predicts a more severe course.[29] It is thought that early diagnosis and treatment may mitigate adverse effects of depression on education, career, and relationships.

It is important to note that secondary depression that is similar to a primary mood disorder may be triggered by serious physical illness such as cancer, stroke, demyelinating diseases, epilepsy, or even marked anemia. Conversely, major depression may be missed when patients present to primary care physicians with predominantly somatic symptoms, including pain.[30] Typically, symptoms such as anorexia, weight loss, constipation, disturbed sleep, anergia, loss of libido, vague aches and pains, and deficiencies in memory and concentration may result in a missed diagnosis, particularly if the patient does not spontaneously report low mood or other psychological symptoms, such as guilt, hopelessness, anxiety, suicidal ideation, or prior suicide attempts. Delusions of guilt and somatic illness complicate up to 14 percent of major depressive episodes, especially postpartum depression.[31]

Depressive episodes in bipolar disorder may be similar to those in major depressive disorder or may present as part of a mixed state characterized by distressing combinations of depression and mania or hypomania (irritability, racing thoughts, anxiety, suicidal thoughts, and aggressive impulses). Patients with bipolar disorder who present with a depressive episode may be misdiagnosed as having major depressive disorder because they may

often underreport hypomanic and manic symptoms, perceiving such features to be closer to well-being than illness. A family history of bipolar disorder can assist in making the correct diagnosis.

ANTIDEPRESSANT MEDICATIONS

About half of moderate-to-severe episodes of depression will improve with antidepressant treatment.[32] Classes of antidepressant agents are defined by their mechanism of action (Table 1). Many agents with effective antidepressant action amplify serotonin or norepinephrine signaling by inhibiting reuptake at the synaptic cleft (Fig. 1A and 1B). The several classes of drugs include SSRIs, norepinephrine-reuptake inhibitors, and dual-action agents that inhibit uptake of serotonin and norepinephrine. Monoamine oxidase inhibitors (MAOIs) inhibit monoamine degradation by monoamine oxidase A or B. Other antidepressant agents antagonize α_2–adrenergic autoreceptors with a resultant increase in the release of norepinephrine, antagonize 5-hydroxytryptamine$_{2A}$ (5-HT$_{2A}$) receptors, or both.

SSRIs

Clinical trials have shown little difference in efficacy or tolerability among various available SSRIs[32-34] or between SSRIs and other classes of antidepressants.[32,35-38] However, some specific differences should be noted.

The active metabolite of fluoxetine has a half-life that is longer than that of other SSRIs, which permits once-daily dosing and thereby reduces the effect of missed doses and mitigates the SSRI discontinuation syndrome (described below). However, fluoxetine should be used with caution in patients with bipolar disorder or a family history of bipolar disorder, because an active metabolite persists for weeks and may aggravate the manic state in the event of a switch from depression to mania. At higher doses, paroxetine and sertraline also block dopamine reuptake, which may contribute to their antidepressant action.

SSRIs can be helpful in patients who do not have a response to tricyclic antidepressants, an older class of drugs, and appear to be better tolerated with lower rates of discontinuation[32,36,37,39] and fewer cardiovascular effects.[39] Although tricyclic antidepressants may have greater efficacy than SSRIs in severe major depressive disorder or depression with melancholic features, they are less effective than SSRIs for bipolar depression, since they can trigger mania or hypomania.[40] SSRIs appear to be less effective than either tricyclic antidepressants or selective norepinephrine-reuptake inhibitors for depression in which physical symptoms or pain is prominent.[41] The SSRI fluoxetine is the only antidepressant that has consistently been shown to be effective in children and adolescents,[42] and SSRIs may be superior to selective norepinephrine-reuptake inhibitors in young adults (18 to 24 years of age),[43] although they are more likely to trigger mania in children.[44]

NOREPINEPHRINE-REUPTAKE INHIBITORS

Nortriptyline, maprotiline, and desipramine are tricyclic norepinephrine-reuptake inhibitors with anticholinergic effects.[45] Reboxetine is a selective norepinephrine-reuptake inhibitor with an effectiveness similar to that of tricyclic antidepressants and SSRIs,[32] though it is unavailable in the United States.

DUAL-ACTION ANTIDEPRESSANTS

Serotonin–norepinephrine reuptake inhibitors such as venlafaxine, duloxetine, and milnacipran block monoamine transporters more selectively than tricyclic antidepressants and without the cardiac-conduction effects that can occur with tricyclic agents.[32] Some tricyclics (imipramine and amitriptyline) inhibit both serotonin and norepinephrine reuptake. The dual-action antidepressant venlafaxine appears to demonstrate superior efficacy and higher rates of remission in severe depression as compared with either SSRIs such as fluoxetine or tricyclic antidepressants.[46-48] The efficacy of duloxetine is similar to that of the SSRI paroxetine.[49] Venlafaxine and duloxetine are effective for the treatment of chronic pain[50] and diabetic neuropathic pain, respectively,[51] as well as pain occurring as part of primary or secondary depression.[52,53] Bupropion, which inhibits both norepinephrine and dopamine reuptake, has no direct action on the serotonin system and is generally similar in efficacy to tricyclic antidepressants[32] and SSRIs.[54] Bupropion is associated with less nausea, diarrhea, somnolence, and sexual dysfunction than are SSRIs[54] and constitutes an effective alternative, or adjunctive therapy, for patients who do not have a response to SSRIs.[55,56]

Table 1. **Classification, Doses, Safety, and Side Effects of Antidepressants.***

Mechanism of Action and Functional Classification	Starting Dose	Standard Dose	Lethality in Overdose	Side Effects						
				Insomnia and Agitation	Sedation	Hypotension	Anticholinergic Effects†	Nausea or Gastrointestinal Effects	Sexual Dysfunction	Weight Gain
	mg/day									
Reuptake inhibitors										
Selective serotonin- reuptake inhibitors (SSRIs)										
Fluoxetine (Prozac)	20	20–40	Low	Moderate	None or mild	None or mild	None or mild	Moderate	Moderate	Mild
Paroxetine (Paxil)	20	20–40	Low	Moderate	None or mild	None or mild	Mild	Moderate	Moderate	Mild
Sertraline (Zoloft)	50	50–150	Low	Moderate	None or mild	None or mild	None or mild	Moderate	Moderate	Mild
Fluvoxamine (Luvox)	50	100–250	Low	Moderate	Mild	None or mild	None or mild	Moderate	Moderate	Mild
Citalopram (Celexa)	20	20–40	Low	Moderate	None or mild	None or mild	None or mild	Moderate	Moderate	Mild
Escitalopram (Lexapro)	10	10–20	Low	Moderate	None or mild	None or mild	None or mild	Moderate	Moderate	Mild
Selective norepinephrine-reuptake inhibitors (NRIs)										
Reboxetine (Edronax)‡	4–8	8–12	Low	Mild	None or mild	None or mild	None or mild	Mild	Mild	None or mild
Nonselective norepinephrine-reuptake inhibitors										
Desipramine (Norpramine)	25–50	100–300	High	Mild	None or mild	Moderate	Mild	None or mild	Mild	Mild
Nortriptyline (Pamelor)	25–50	75–200	High	Mild	Mild	Mild	Mild	None or mild	Mild	Mild
Maprotiline (Ludiomil)	75	75–200	High	Mild	None or mild	Mild	Mild	None or mild	Mild	Moderate
Mixed or dual-action reuptake inhibitors										
Older agents (TCAs)										
Amitriptyline (Elavil)	25–50	100–300	High	None or mild	Moderate	Moderate	Severe	None or mild	Mild	Moderate
Dothiepin (Dothep)‡	25–50	100–300	High	None or mild	Moderate	Moderate	Moderate	None or mild	Mild	Moderate
Clomipramine (Anafranil)	25–50	100–250	High	Mild	Moderate	Moderate	Moderate	Mild	Mild	Moderate
Imipramine (Tofranil)	25–50	100–300	High	Moderate	Mild	Moderate	Moderate	None or mild	Mild	Moderate

Newer agents (non-TCAs)										
Venlafaxine (Effexor) (NRI plus SRI)	37–75	75–225	Moderate	Moderate	None or mild	None or mild	None or mild	Moderate	Moderate	None or mild
Milnacipran (Ixel) (NRI plus SRI)‡	50–100	100–200	Low	Moderate	None or mild	None or mild	None or mild	Moderate	Moderate	None or mild
Bupropion (Wellbutrin) (NRI plus DRI)	150	150–300	Low	Moderate	None or mild	None or mild	Mild	Mild	None or mild	None or mild
Duloxetine (Cymbalta) (NRI plus SRI)	30	30–90	Low	None or mild	Mild	None or mild	Mild	Mild	None or mild	None or mild
MAOIs										
Irreversible agents										
Phenelzine (Nardil)	15	30–90	High	Moderate	Mild	Moderate	Mild	Mild	Moderate	Mild
Tranylcypromine (Parnate)	10	20–60	High	Moderate	Mild	Moderate	Mild	Mild	Moderate	Mild
Isocarboxazid (Marplan)	20	20–60	High	Moderate	None or mild	Moderate	Mild	Mild	Moderate	Moderate
Selegiline (Eldepryl)	10	20–40	Moderate	Mild	None or mild	Mild	Mild	Mild	Mild	Mild
Reversible agents										
Moclobemide (Manerix)‡	150	300–600	Low	Mild	None or mild	None or mild	Mild	Mild	None or mild	None or mild
Mixed-action newer agents										
Mirtazapine (Remeron) (5-HT_2 plus 5-HT_3 plus α_2-adrenergic receptors)	30	30–60	Low	None or mild	Severe	Mild	None or mild	None or mild	None or mild	Severe
Mianserin (Bolvidon) (5-HT_2 plus α_1- and α_2-adrenergic receptors)‡	30	60–120	Low	None or mild	Moderate	Mild	Mild	None or mild	None or mild	Mild
Nefazodone (Serzone) (5-HT_2 receptors)	100	300–600	Low	None or mild	Moderate	Mild	Mild	Mild	None or mild	Mild
Trazodone (Desyrel) (5-HT_2 plus α_1-adrenergic receptors)	50–100	200–600	Low	None or mild	Severe	Mild	None or mild	Mild	Moderate	Mild

* These doses are standard in psychiatric practice but may not always conform to doses recommended in the *Physician's Desk Reference* or drug package insert. More detailed reviews of side effects for all classes of antidepressants may be found in the Guidelines of the American Psychiatric Association 2000 and the Agency for Health Care Policy and Research 1999. NRI denotes norepinephrine-reuptake inhibitor, TCA tricyclic antidepressant, SRI serotonin-reuptake inhibitor, MAOI monoamine oxidase inhibitor, and DRI dopamine-reuptake inhibitor.

† Symptoms include dry mouth, constipation, sweating, blurred vision, and urinary retention.

‡ This drug is not available in the United States.

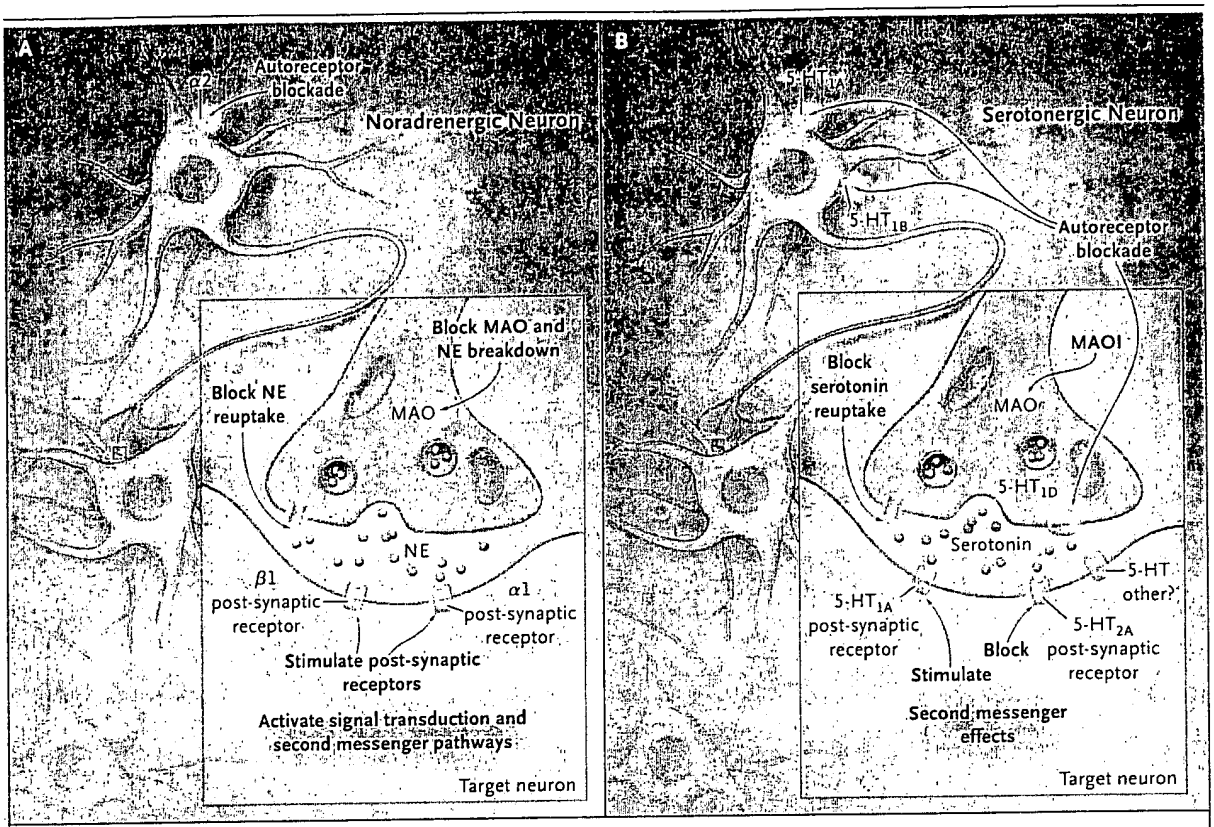

Figure 1. **Targets of Antidepressant Action on Noradrenergic and Serotonergic Neurons.**

In Panel A, targets of action for antidepressants in the noradrenergic system can enhance activity by blockade of the α_2-adrenergic autoreceptor, blockade of norepinephrine (NE) reuptake at the synaptic cleft, stimulation of α_1-adrenergic and β_1-adrenergic postsynaptic receptors, activation of signal transduction and second-messenger pathways, and blockade of monoamine oxidase (MAO), the enzyme involved in NE breakdown. In Panel B, targets of action for antidepressants in the serotonergic system can enhance activity by blockade of 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} autoreceptors; blockade of serotonin reuptake at the synaptic cleft; activation of the 5-HT_{1A} postsynaptic receptor; activation of signal transduction and second-messenger pathways; and blockade of the 5-HT_{2A} postsynaptic receptor. Monoamine oxidase inhibitors (MAOIs) function by blockade of MAO, the enzyme involved in serotonin breakdown.

MAOIs

Older, irreversible MAOIs nonselectively block MAO A and B isoenzymes and have an antidepressant efficacy similar to that of tricyclic antidepressants. However, MAOIs are not first-line drugs because patients who receive them must adhere to a low-tyramine diet to prevent hypertensive crisis and because MAOIs carry greater drug-interaction risks than do other medications. MAOIs appear to be superior to tricyclic agents for people with depression characterized by extreme fatigue or extreme psychological sensitivity to rejection or failed relationships.[57] MAOIs are also useful for treating patients who do not have a response to tricyclic antidepressants.[58] The reversible selective MAO A inhibitor moclobemide (which is not available in the United States but widely available in other countries) and the MAO B-selective inhibitor, selegiline, have a greater safety margin than do SSRIs but similar efficacy.[59,60] A selegiline transdermal patch is under consideration by the Food and Drug Administration (FDA).

OTHER ANTIDEPRESSANTS AND NEW THERAPIES

Mirtazapine enhances the release of norepinephrine by blocking α_2-adrenergic autoreceptors as well as serotonin 5-HT_{2A} and 5-HT_3 receptors and histamine H_1 receptors. Its efficacy is similar to that of tricyclic antidepressants and SSRIs,[61] and it is less likely to have sexual and sleep-related side effects.[62,63]

Nefazodone, which blocks the 5-HT_{2A} seroto-

nin receptor and serotonin reuptake, has an antidepressant efficacy similar to that of SSRIs but with a lower likelihood of sexual-dysfunction and sleep-related side effects.[64,65] Nefazodone appears to be useful in postpartum depression,[66] severe depression,[67] and treatment-resistant major depression with anxiety.[68]

New antidepressive treatments currently being evaluated include vagal-nerve stimulation, rapid transcranial magnetic stimulation, mifepristone (a glucocorticoid antagonist for treatment of delusional depression), and substance P antagonists. Other targets for future agents include neuropeptide Y, vasopressin V1b, *N*-methyl-D-aspartate, nicotinic cholinergic, delta-opiate, cannabinoid, dopamine D1, cytokine, and corticotropin-releasing factor 1 receptors, as well as GABA, intracellular messenger systems, and transcription, neuroprotective, and neurogenic factors.

AUGMENTING AND ADJUNCTIVE MEDICATIONS

Various medications used in conjunction with other antidepressants may help to augment the effect of antidepressants (Table 2). They can also target different components of patients' symptoms (such as delusions) or help to prevent a switch into mania.

MOOD STABILIZERS

Lithium is an antimanic agent and, as a mood stabilizer, prevents the recurrence of mania or depression. It may be superior to placebo for bipolar depression but not for major depression.[69] Lithium is an effective augmenting agent, and the condition of roughly half the patients who do not have a response to a single antidepressant improves when lithium is added.[70,71]

The anticonvulsant lamotrigine reduces glutamatergic activity and has been used as an augmenting agent in major depressive disorder[72] and for treating and preventing depressive relapse in bipolar disorder.[73] Lamotrigine can induce severe skin reactions, including the Stevens–Johnson syndrome and toxic epidermal necrolysis, although gradual dose titration appears to reduce the risk.

Other mood stabilizers, including the anticonvulsants valproic acid, divalproex, and carbamazepine, are used to treat mania in bipolar disorder. Divalproex or valproate may prevent a recurrence of bipolar depression.[74]

ANTIPSYCHOTIC AGENTS

Typical antipsychotic agents (e.g., chlorpromazine, fluphenazine, and haloperidol) block the dopamine D2 receptor, whereas "atypical" antipsychotic agents (e.g., clozapine, olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole), like nefazodone, act as $5HT_{2A}$ antagonists. Antipsychotic drugs are combined with antidepressants to treat depression with psychotic features.[75,76] Atypical antipsychotic drugs are also used for treatment-resistant major depression[77] and bipolar depression.[78]

Although atypical antipsychotic drugs have a more favorable side-effect profile with respect to parkinsonism, akathisia, and tardive dyskinesia, some pose other risks, such as drug-induced arrhythmia, diabetes, weight gain, and hyperlipidemia.[79,80]

OVERALL THERAPEUTIC STRATEGY

Patients who present with the complex, variable clinical picture of major depressive disorder and bipolar disorder may require a multimodal approach that includes pharmacotherapy, education, and psychotherapy. Treatment requires the monitoring of clinical responses, including suicidal ideation or behavior and side effects. To encourage adherence to therapy, education of both patients and their families must emphasize the fact that the effects of antidepressant medication take time. The average treatment duration for an episode is six months, and there is a high risk of future episodes; thus, both patients and their families must be made aware of these facts. The treatment plan should take into account the patient's previous treatment outcomes, the mood-disorder subtype, the severity of the current episode of depression, the risk of suicide, coexisting psychiatric and somatic conditions, nonpsychiatric medications, and psychosocial stressors.[45] There are three phases of treatment: the acute, continuation, and maintenance phases.

ACUTE PHASE

The treatment goal in the acute phase is remission — the induction of a state with minimal symptoms — in which the criteria for a major depressive episode have abated and marked improvement in psychosocial functioning has occurred, on the basis of reports from the patient and the patient's family. Figure 2 presents a basic algorithm for the acute

Table 2. Augmenting or Adjunctive Drugs.*

Drug	Starting Dose	Standard Dose	Main Side Effects					
			Weight Gain	Lethargy	Ataxia	Nausea	Tremor	Other
	mg/day							
Mood stabilizers								
Lithium	600–900	450–1500	Severe	Mild	None or mild	Moderate	Severe	Polyuria, fatigue, hypothyroidism, cognitive deficits, acne, headache, worsens psoriasis
Lamotrigine (Lamictal)	25	50–300	Mild	Moderate	Moderate	Moderate	None or mild	Dizziness, headache, insomnia, severe skin reactions (e.g., Stevens–Johnson syndrome)
Valproic acid (Depakene) or divalproex (Depakote)	15 per kg of body weight	Up to 60 per kg of body weight	Moderate	Moderate	Moderate	Moderate	Severe	Headache, ovarian cysts
			Weight Gain	Sedation	Diabetes or Lipid Increase	Tardive Dyskinesia	Hypotension	
Antipsychotic agents								
Typical								
Chlorpromazine (Thorazine)	25	75–200	Moderate	Severe	None or mild	Severe	Mild	EPS, sinus tachycardia
Haloperidol (Haldol)	2–6	10–20	None or mild	None or mild	None or mild	Severe	Mild	EPS, akathisia, sinus tachycardia
Atypical								
Clozapine (Clozaril)	25	300–400	Severe	Severe	Moderate	None or mild	Severe	Low white-cell count
Olanzapine (Zyprexa)	5	10–20	Severe	Mild	Moderate	Mild	Mild	EPS, hepatic effects, dizziness
Risperidone (Risperdal)	1–2	4–6	Mild	Mild	None or mild	Mild	Mild	EPS, insomnia, agitation, CVA in dementia
Quetiapine (Seroquel)	50	300–600	Mild	Mild	Mild	Mild	Moderate	Somnolence, dizziness, dyspepsia
Aripiprazole (Abilify)	10–15	15–30	None or mild	Mild	None or mild	Mild	Mild	EPS, insomnia, agitation, anxiety
Ziprasidone (Geodon)	40–80	80–160	None or mild	Mild	None or mild	Mild	Mild	EPS, constipation, fatigue, insomnia, QT prolongation
Thyroid supplement								
Thyroxin (Synthroid)	0.05	0.05–0.1	NA	NA	NA	NA	NA	None if thyroid function is monitored

* These doses are standard in psychiatric practice but may not always conform to doses recommended in the *Physicians' Desk Reference* or in drug package inserts. EPS denotes extrapyramidal syndrome, CVA cardiovascular accident, and NA not applicable.

phase of treatment of a major depressive episode in a patient with major depressive disorder, on the basis of the current literature and treatment models, which were developed as part of several large-scale studies of treatment algorithms.[81-83] Hospitalization is needed if symptoms are severe (dehydration, delusions, and psychomotor agitation) and there is a risk of suicide (previous suicide attempts or current plan for suicide).

Antidepressants are the treatment of choice for moderate-to-severe episodes of depression. Since most antidepressants that are used for major de-

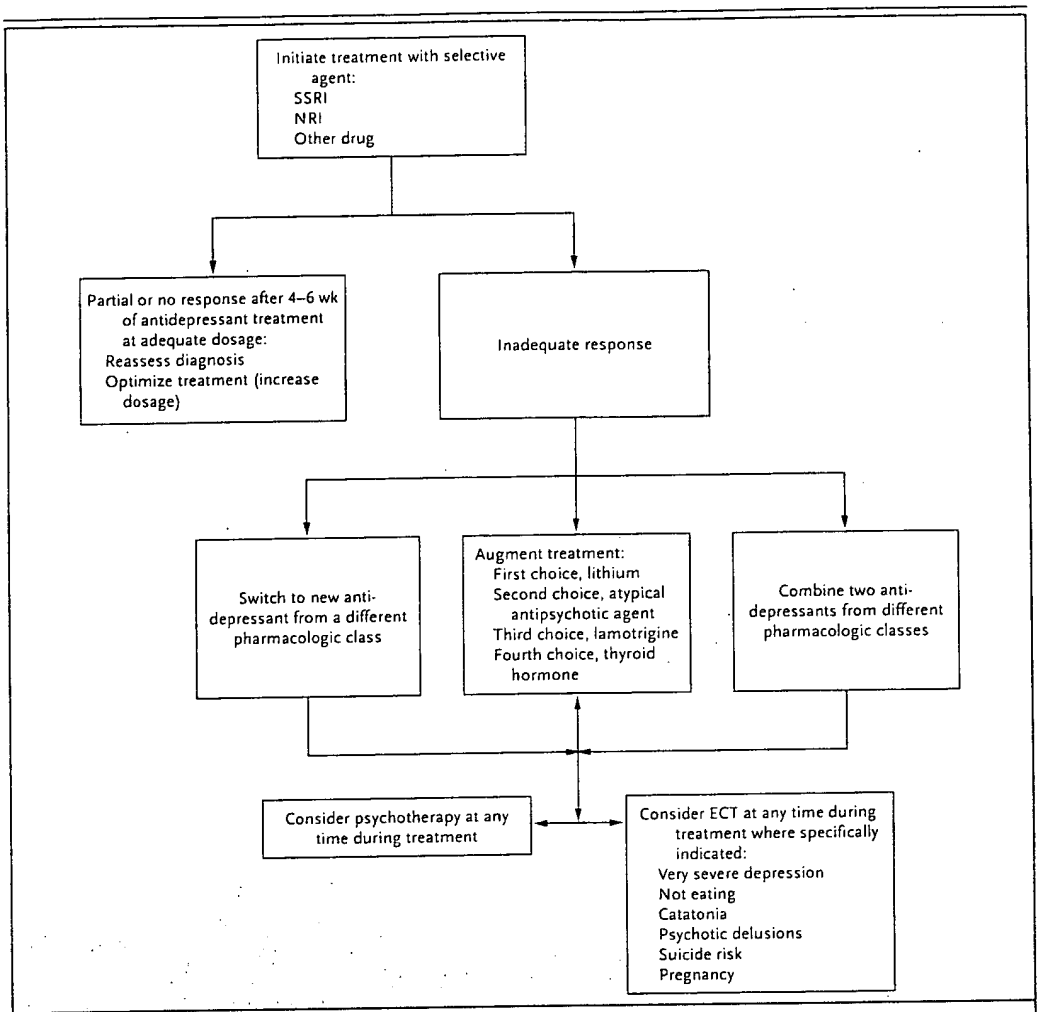

Figure 2. Algorithm for the Acute Treatment Phase of a Major Depressive Episode in Major Depressive Disorder.
SSRI denotes selective serotonin-reuptake inhibitor, NRI norepinephrine reuptake inhibitor, and ECT electroconvulsive therapy.

pressive disorder have similar effectiveness, the choice of medication depends on depressive symptoms (psychotic or suicidal), the history of responses to medication (including that of first-degree relatives), medication tolerability, adverse effects, and the likelihood of adherence. Other considerations are concurrent medical conditions, use of nonpsychiatric drugs, and cost of medication. Table 3 lists suggested first-line medications.

SSRIs and other newer antidepressant drugs with a greater safety margin constitute first-line medications for moderate-to-severe depression, particularly for outpatients, for patients treated by primary care physicians, and for patients with cardiovascular disease.[45,84] Depression in persons 65 years of age or older generally requires relatively low doses of antidepressants,[85] and SSRIs appear to be preferable to nonselective norepinephrine-reuptake inhibitors, such as tricyclic antidepressants, because of the lower risk of anticholinergic and cardiovascular side effects.[39]

The acute treatment phase usually lasts 6 to 10 weeks (Table 1). The patient should be evaluated weekly or twice monthly by the treating physician until substantial improvement is achieved. Doses should be low initially and gradually increased, depending on the clinical response (Table 4) and side effects. The decision to increase the dose, change

Table 3. **Selection of a First-Line Antidepressant Medication.***

Variable	Medication
Patient history	
Age group	
Children and adolescents	SSRI (fluoxetine)
Adults <65 yr	SSRI, NRI, or SNRI
Adults ≥65 yr	SRI
Family history of response	Same medication that was effective in first-degree relative
Past response	Same medication that was effective previously
Depression characteristic	
Bipolar depression	Mood stabilizer (lithium or lamotrigine) plus antidepressant
Psychotic depression	Antidepressant plus antipsychotic (atypical)
Depression with features of obsessive–compulsive disorder	SSRI
Panic attacks	SSRI
Agitated depression	Sedating antidepressant
Depression with psychomotor retardation	Nonsedating antidepressant (NRI, SSRI)
Medication-resistant depression	Electroconvulsive therapy or combination of medications
Coexisting medical conditions	
Heart disease	Nontricyclic antidepressants
Stroke	Caution with SNRIs or NRIs and blood pressure
Pain	Duloxetine, venlafaxine
Concern regarding side effects	
Gastrointestinal symptoms	Nontricyclic antidepressant
Anticholinergic symptoms	Nontricyclic antidepressant
Sexual dysfunction	Non-SSRI antidepressant
Weight gain	Avoid atypical antipsychotics
Postural hypotension	NRI
Diabetes	Avoid atypical antipsychotics

* SSRI denotes selective serotonin-reuptake inhibitor, SNRI serotonin–norepinephrine reuptake inhibitor, NRI norepinephrine-reuptake inhibitor, and SRI serotonin-reuptake inhibitor.

the medication, or add another medication is modeled in Figure 2. Outpatients at risk for suicide should not be given large supplies of antidepressant drugs that could be lethal in the case of an overdose (Table 1).

MONITORING TREATMENT RESPONSE

The response of patients to treatment requires systematic monitoring. A practical set of criteria include nonresponse, a decrease in baseline severity of 25 percent or less; partial response, a 26 to 49 percent decrease in baseline severity; partial remission, a 50 percent or greater decrease in baseline severity (residual symptoms); and remission, an absence of symptoms. Options for the evaluation of the response include rating scales (Table 4) and the global judgment of the treating clinician on the basis of patient and family reports. The best predictors of outcome are improvements in anhedonia (loss of pleasure), psychomotor retardation, and loss of interest, which are assessed by asking questions that go beyond "depressed mood." Suicidal ideation or risk of suicide, pessimism, guilt, and other changes in cognition may take longer to improve than vegetative symptoms, such as alterations in sleep or appetite.[86] If initial treatment is not tolerated or the response is unsatisfactory (<50 percent improvement), a change in medication or approach is indicated. Thirty to 50 percent of patients have substantial residual symptoms after adequate first-line treatment (Table 3).[87] If there has been no improvement after four weeks of treat-

ment with an adequate dose of a given medication, the ultimate response is almost certainly going to be inadequate.[88]

Among patients receiving the same dose of a given drug, blood levels may vary by as much as a factor of 20 because of individual variations in drug metabolism. Such variations are caused by genetic differences, the effects of drugs on liver enzymes, and the effects of aging. Before medications are switched, consideration should be given to the diagnosis, the medication dose, and adherence to the drug regimen. Coexisting medical conditions, alcoholism, substance-use disorder, or the use of nonpsychiatric medications such as beta-blockers may also underlie treatment failures.

Nonresponse to medication requires a treatment change (Fig. 2). Switching to an antidepressant from a different pharmacologic class minimizes polypharmacy and reduces the risk of adverse drug interactions and side effects seen with combinations of similar drugs. The disadvantage of switching agents may be the loss of a possible partial response from the initial drug and a delay in the onset of antidepressant action from the second. The initial medication may need to be tapered to avoid symptoms of discontinuation, such as nausea, headache, and sensory changes. Switching from irreversible MAOIs to most other agents requires a minimum drug-free period of two weeks.

Switching to a new antidepressant from the same pharmacologic class is one option. Patients who do not have a response to one SSRI have a 40 to 70 percent chance of having a response to a second SSRI.[89] Another approach is the use of two antidepressants from different classes with complementary mechanisms of action to avoid loss of a partial response to the first medication. This approach increases the risk of drug interactions and new side effects, as well as the cost of treatment.

Augmenting antidepressant medication with other agents, so-called augmenting agents, that may enhance antidepressant efficacy avoids the transition from the first to the second antidepressant and builds on partial remission. Lithium is a first-line augmenting agent.[90] Two to four weeks of lithium treatment are needed before the response can be assessed. Lamotrigine is an effective augmenting agent for patients who do not have an adequate response to fluoxetine.[72] Antipsychotic agents may augment the response in nonpsychotic major depression.[91] Thyroid supplements have been advocated even in the absence of clinical hypothyroidism for the purpose of enhancing antidepressant action. Modafinil is a stimulant and as an adjunct may alleviate residual sleepiness and fatigue.[92]

Table 4. **Assessment of the Response to Antidepressant Treatment.***

Variable	Response
Nonresponse	Minimal or <25% decrease in baseline severity of symptoms
Partial response	Reduction in severity of symptoms but symptoms still in evidence; 26–49% decrease in baseline severity of symptoms
Partial remission	Most symptoms not in evidence, but still some residual symptoms; ≥50% decrease in baseline severity of symptoms
Remission	No symptoms; return to normal functioning
Relapse	Return to fully symptomatic state while patient is in remission
Recovery	Extended remission
Recurrence	Onset of a new episode of depression when patient is in recovery

* Several scales are available for the assessment of baseline symptoms or functioning and subsequent response, including the Hamilton Depression Rating Scale, Global Assessment Scale, Beck Depression Inventory, Clinical Global Impressions Scale, and Montgomery–Asberg Depression Rating Scale.

Mood disorders with delusions or hallucinations respond better to an antidepressant–antipsychotic combination than to either alone.[93] Some patients with this constellation of symptoms will require electroconvulsive therapy (ECT), and almost all must be treated initially as inpatients.

Benzodiazepines are used as an adjunct for anxiety and insomnia in 30 to 60 percent of cases, and in that group improve response and reduce the frequency of treatment discontinuation.[94] However, the drugs cause sedation, psychomotor and cognitive impairment, memory loss, and dependence and withdrawal syndromes and are associated with increased rates of falls, fractures, traffic accidents, and death among the elderly.[95,96] The adjunctive use of benzodiazepines should be of limited duration to avoid dependence, and these drugs should be used with caution in the elderly and those with a history of alcohol or drug abuse or dependency.

CONTINUATION PHASE

The continuation phase of treatment, generally lasting six to nine months after the induction of remission, aims to eliminate residual symptoms, restore the prior level of functioning, and prevent recurrence or early relapse. Residual symptoms (partial remission) are strong predictors of recurrence, early relapse, or a more chronic future course.[97] Treatment should continue until such symptoms have resolved. Episodes lasting more

than 6 months and psychotic depression require a longer continuation phase, up to 12 months.[88] The same medications and doses used to achieve relief in the acute phase are used during the continuation phase.[45]

DISCONTINUATION OF TREATMENT

If there is no recurrence or relapse during continuation therapy, gradual discontinuation may be planned for most patients after at least six months of treatment. Early discontinuation is associated with a 77 percent higher risk of relapse as compared with continuation treatment.[98] The tapering of medication over several weeks also permits detection of returning symptoms that require reinstitution of a full medication dose for another three to six months. It also minimizes the discontinuation syndrome, which otherwise may last days or longer and consists of physical symptoms of imbalance, gastrointestinal and influenza-like symptoms, and sensory and sleep disturbances, as well as psychological symptoms such as anxiety, agitation, crying spells, and irritability.[99] The discontinuation syndrome is sometimes called the withdrawal syndrome, erroneously implying drug dependence.

MAINTENANCE PHASE

Maintenance treatment for 12 to 36 months reduces the risk of recurrence by two thirds.[100] This approach is indicated for patients with episodes that occur yearly, who have impairment because of mild residual symptoms, who have chronic major depression or dysthymia, or who have extremely severe episodes with a high risk of suicide.[8,45,97] The duration of maintenance treatment will depend on the natural history of the illness and may be prolonged or indefinite in the case of recurrent illness.

The first choice of medication for the maintenance phase is the antidepressant that brought about remission.[45] Lithium has no advantage over antidepressants for prophylaxis[69] but may reduce the risk of suicide independently of its effect on mood.[101] Tricyclic antidepressants, SSRIs, MAOIs, and the newer antidepressants (mirtazepine and venlafaxine) all help to prevent recurrence.[69,101-104] Medication tolerability is particularly important during the maintenance phase, because it affects patients' adherence to treatment. Stable patients should see a psychopharmacologist at intervals of three to six months while they are receiving medication. It is important to monitor adherence and breakthrough symptoms so that problems are detected early. Patient and family education reduces treatment attrition and improves the outcome.

NONPHARMACOLOGIC THERAPIES

ECT

Remission rates with ECT are 60 to 80 percent in severe major depressive disorder,[105] though lower success rates are reported in community settings.[106] The maximum response is typically achieved within three weeks. ECT can be a first-line treatment for patients who have severe major depressive disorder with psychotic features, psychomotor retardation, or medication resistance.[45] ECT offers rapid relief for patients who are suicidal or pregnant.[45] A course of ECT usually consists of 6 to 12 treatments, rarely exceeds 20 treatments, and is administered two or three times a week, preferably by an experienced psychiatrist. Side effects include transient postictal confusion and anterograde and retrograde memory impairment; the latter generally improves in days or weeks.[107] After ECT, it is important to start prophylactic treatment with an antidepressant medication combined with an augmenting medication such as lithium, because the relapse rate is more than 50 percent.[108]

PSYCHOTHERAPY

Brief, structured psychotherapy techniques — such as cognitive behavioral therapy, interpersonal therapy, and certain problem-solving therapies — appear to be effective in acute-phase treatment and to delay relapse during continuation treatment of mild to moderately severe depression.[45,109,110] Psychotherapy can be a first-line therapy for mild depression but not for severe depression, particularly psychotic and bipolar forms, unless used in combination with pharmacology.[45,111] A combination of pharmacotherapy and psychotherapy may improve the treatment response, reduce the risk of a relapse, enhance the quality of life, and increase adherence to pharmacotherapy.[112] Psychotherapy should be considered when substantial psychosocial stressors, interpersonal difficulties, or coexisting developmental or personality disorders are present.

SPECIAL PATIENT POPULATIONS

PATIENTS WITH BIPOLAR DISORDER

Depression in bipolar disorder carries the risk of a switch into mania.[113,114] Mood stabilizers with antidepressant properties, such as lithium and la-

motrigine, help prevent mania, hypomania, and mixed or rapid-cycling states[115,116] and are recommended as initial treatments of bipolar depression.[103] For severe bipolar depression, a combination of an antidepressant (an SSRI or bupropion) and a mood stabilizer should be considered from the outset.[40,117,118] The atypical antipsychotic drugs olanzapine and risperidone have antidepressant and antimanic effects[119] but are more effective when combined with an antidepressant.[120] The American Psychiatric Association recommends maintenance treatment after a single manic episode.[103]

CHILDREN AND ADOLESCENTS

Fluoxetine is the only antidepressant with demonstrated efficacy in childhood and adolescent depression[42]; other SSRIs, tricyclic agents, and other new-generation antidepressants have not been shown to be effective for depression in this age group.[121] Fluoxetine is the only SSRI currently approved for pediatric use.

Rates of spontaneously reported suicidal ideation and suicide attempts have been higher among depressed children and adolescents receiving antidepressants than among those receiving placebo in controlled clinical trials, but no differences were noted on weekly ratings of suicidality. This possible risk needs to be weighed against the risk of untreated depression, the most common cause of suicide in youth.[122] There is an FDA black-box warning urging clinicians to monitor suicide risk and side effects very carefully when using antidepressants in youth (www.fda.gov/cder/drug/antidepressants/default.htm).

PREGNANT WOMEN

Antidepressant medication should be considered for pregnant women in whom a moderately severe major depressive disorder develops spontaneously, as well as for those at high risk for recurrence if their medication is discontinued.[45] Risks and benefits vary greatly among patients.[123] Many antidepressants are transmitted in breast milk, and their use is reviewed elsewhere.[124]

SUMMARY

Major depression and bipolar disorder are generally recurrent episodic disorders. Antidepressant and adjunctive medications can successfully treat depression and prevent future episodes.

Future challenges include the identification of antidepressants that act more quickly than those currently available, which take six to eight weeks to achieve remission or substantial improvement, and that do not require continuation and maintenance treatment. A biologic classification system of subtypes of major depression is needed to facilitate the selection of the best antidepressant for each patient.

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